

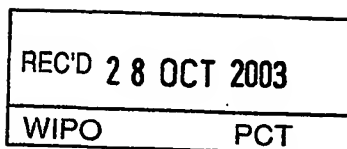


PCT/GB2003/03936

Rec'd PCT/PTO 14 MAR 2005  
10/527910 #2

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# Patents Form 1/77

## Request for grant of a patent

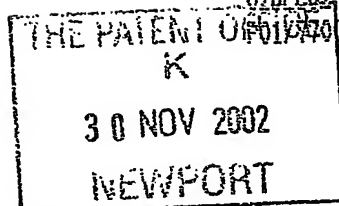
The Patent Office

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02DEC02 5767744-1 D02846

Newport

NP9 1RH



1. Your Reference

DPW/HMC/W823

2. Application number

0228018.8

30 NOV 2002

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(if applicable)

4. Title of the invention

CARBONYLATION OF ESTER

5. Name of agent

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Address for service in the UK to  
which all correspondence should  
be sent

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Patents ADP number

190001

6. Priority claimed to:

Country

Application number

Date of filing

7. Divisional status claimed from:

Number of parent application

Date of filing

8. Is a statement of inventorship and  
of right to grant a patent required in  
support of this application?

YES

9. Enter the number of sheets for any of the following items you are filing with this form. Do not count copies of the same document

Continuation sheets of this form

Description

35



Claim(s)

Abstract

Drawing(s)

10. If you are also filing any of the following, state how many against each item

Priority documents

Translation of priority documents

Statement of inventorship and right to grant a patent (PF 7/77)

Request for a preliminary examination and search (PF 9/77)

Request for substantive examination (PF 10/77)

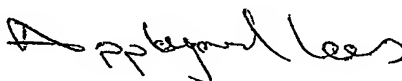
Any other documents (please specify)

- 11.

We request the grant of a patent on the basis of this application.  
Signature Date

APPLEYARD LEES

29 November 2002



12. Contact

David P Walsh- 01422 330110

## Carbonylation of Ester

The present invention relates to the carbonylation of an ester, specifically vinyl acetate and in particular but not exclusively the use of the carbonylation to provide a first step in the production of methyl lactate and 3-hydroxymethyl propanoate.

Currently methyl lactate is produced by esterification of lactic acid, which is produced either by synthetic methods or fermentation.

10

The main synthetic routes are based on the reactions of acetaldehyde. In one method, acetaldehyde is reacted with hydrogen cyanide to produce a lactonitrile, which is then hydrolysed. Alternatively, acetaldehyde can be reacted with carbon monoxide and water in the presence of a nickel (II) iodide or sulphuric acid catalyst. Synthetic routes produce racemic mixtures of lactic acid, and so racemic mixtures of methyl lactate result. In recent years, improvements in fermentation methods have made this a preferred route to lactic acid and its derivatives. Optically pure lactic acid can be produced by the fermentation of sugars with carefully chosen bacteria. Lactobacilli tend to be heat resistant, so fermentation at temperatures of around 50°C suppresses secondary reactions. The procedure is slow, and requires careful monitoring of pH, temperature and oxygen levels, but by selecting an appropriate bacteria culture, optically pure lactic acid, of both R and S forms can be produced.

15

20

Methyl lactate is used as a high boiling point solvent, and is present in a variety of materials such as detergents, degreasing agents, cosmetics and food flavourings. It is biodegradable, and so environmentally friendly.

25

A route to 1, 3-propanediol would be industrially favourable, as there is currently not a route to the diol that is commercially viable. In the 1980s, Davy Process Technology found a route to 1, 4-butanediol, by forming diethyl maleate from butanes over a solid acid catalyst, and then dehydrogenating it to the diol. 1, 4-butanediol is now widely used as a polymer component and also in fibre production and as a high boiling solvent. Polyhydric alcohols are often used in reactions with isocyanates to produce urethanes, and in reactions with acids and acid anhydrides to produce (poly) esters. 1, 3-propanediol is thought to have uses as a polymer component and as a high boiling point solvent.

30

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The carbonylation of ethylenically unsaturated compounds using carbon monoxide in the presence of an alcohol or water and a catalyst system comprising a group VIII metal, example, palladium, and a phosphine ligand, example an alkyl phosphine, cycloalkyl phosphine, aryl phosphine, pyridyl phosphine or bidentate phosphine, has been described in numerous European patents and patent applications, example EP-A-0055875, EP-A-04489472, EP-A-0106379, EP-A-0235864, EP-A-0274795, EP-A-0499329, EP-A-0386833, EP-A-0441447, EP-A-0489472, EP-A-0282142, EP-A-0227160, EP-A-0495547 and EP-A-0495548. In particular, EP-A-0227160, EP-A-0495547 and EP-A-0495548 disclose that bidentate phosphine ligands provide catalyst systems which enable high reaction rates to be achieved.

The main problem with the previously disclosed catalyst systems is that, although relatively high reaction rates can be achieved, the palladium catalyst dies off quickly which is industrially unattractive.

It has been disclosed in WO96/19434 that a particular group of bidentate phosphine compounds can provide remarkably stable catalysts which require little or no replenishment; that use of such bidentate catalysts leads to reaction rates which are significantly higher than those previously disclosed; that little or no impurities are produced at high conversions.

In addition, WO 96/19434 discloses that the same catalyst process when used with respect to propene has been found to be more difficult.

WO 01/68583 discloses rates for the same process used for higher alkenes of C3 or more carbon atoms when in the presence of an externally added aprotic solvent.

EP0495548B1 gives an example of vinyl acetate carbonylation employing the C3 bridged phosphine 1,3bis (di-tert-butylphosphino) propane. The rates quoted are 200 moles product per mole of Pd per hour and the result is the production of 1 and 2 - acetoxy methyl propanoate in a ratio of 40:60 (linear:branched).

WO 01/68583 discloses a high regioselectivity for the linear product when carrying out carbonylation with a bidentate phosphine having an aryl bridge linked to the respective phosphines via adjacent carbons on the ring.

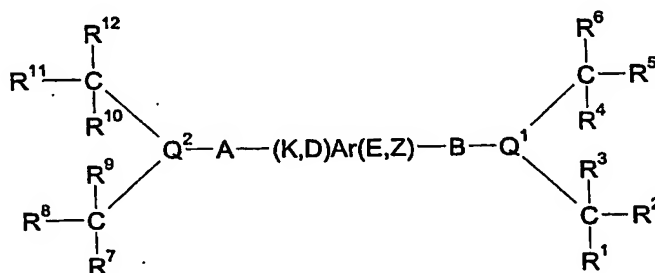
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However, surprisingly, it has been found that the carbonylation of vinyl acetate produces mainly branched product, rather than the linear product obtained with other substrates, with the same bidentate phosphine aryl bridged ligand.

- 5 According to a first aspect of the present invention there is provided a process for the carbonylation of vinyl acetate comprising reacting vinyl acetate with carbon monoxide in the presence of a source of hydroxyl groups and of a catalyst system, the catalyst system obtainable by combining:

- 10 (a) a metal of Group VIII B or a compound thereof: and  
(b) a bidentate phosphine of general formula (I)

(I)



wherein:

- 15 Ar is a bridging group comprising an optionally substituted aryl moiety to which the phosphorus atoms are linked on available adjacent carbon atoms;

A and B each independently represent lower alkylene;

- 20 K, D, E and Z are substituents of the aryl moiety (Ar) and each independently represent hydrogen, lower alkyl, aryl, Het, halo, cyano, nitro, OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)OR<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>, C(O)NR<sup>25</sup>R<sup>26</sup>, C(S)R<sup>25</sup>R<sup>26</sup>, SR<sup>27</sup>, C(O)SR<sup>27</sup>, or -J-Q<sup>3</sup>(CR<sup>13</sup>(R<sup>14</sup>)(R<sup>15</sup>))CR<sup>16</sup>(R<sup>17</sup>)(R<sup>18</sup>) where J represents lower alkylene; or two adjacent groups selected from K, Z, D and E together with the carbon atoms of the aryl ring to which they are attached form a further  
25 phenyl ring, which is optionally substituted by one or more substituents selected from hydrogen, lower alkyl, halo, cyano, nitro, OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)OR<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>, C(O)NR<sup>25</sup>R<sup>26</sup>, C(S)R<sup>25</sup>R<sup>26</sup>, SR<sup>27</sup> or C(O)SR<sup>27</sup> or, when Ar is a cyclopentadienyl group, Z may be represented by -M(L<sub>1</sub>)<sub>n</sub>(L<sub>2</sub>)<sub>m</sub> and Z is connected via a metal ligand bond to the cyclopentadienyl group;

R<sup>1</sup> to R<sup>18</sup> each independently represent lower alkyl, aryl, or Het;

R<sup>19</sup> to R<sup>27</sup> each independently represent hydrogen, lower alkyl, aryl or Het;

5 M represents a Group VIB or VIIB metal or metal cation thereof;

L<sub>1</sub> represents a cyclopentadienyl, indenyl or aryl group each of which groups are optionally substituted by one or more substituents selected from hydrogen, lower alkyl, halo, cyano, nitro, OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)OR<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>, C(O)NR<sup>25</sup>R<sup>26</sup>, C(S)R<sup>25</sup>R<sup>26</sup>, SR<sup>27</sup>, C(O)SR<sup>27</sup> or  
10 ferrocenyl;

L<sub>2</sub> represents one or more ligands each of which are independently selected from hydrogen, lower alkyl, alkylaryl, halo, CO, PR<sup>43</sup>R<sup>44</sup>R<sup>45</sup> or NR<sup>46</sup>R<sup>47</sup>R<sup>48</sup>;

15 R<sup>43</sup> to R<sup>48</sup> each independently represent hydrogen, lower alkyl, aryl or Het;

n = 0 or 1;

and m = 0 to 5;

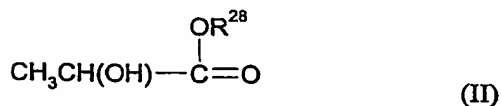
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provided that when n = 1 then m equals 0, and when n equals 0 then m does not equal 0;

Q<sup>1</sup>, Q<sup>2</sup> and Q<sup>3</sup> (when present) each independently represent phosphorous, arsenic or antimony and in the latter two cases references to phosphine or phosphorous above are amended  
25 accordingly.

Preferably, the Group VIII B metal is palladium.

30 According to a second aspect of the present invention there is provided a process for the production of a lactate ester or acid of formula II



comprising the steps of carbonylating vinyl acetate with carbon monoxide in the presence of a source of hydroxyl groups and of a catalyst system, the catalyst system obtainable by combining:

- 5 (a) a metal of Group VIII B or a compound thereof: and
- (b) a bidentate phosphine of general formula (I) in accordance with the first aspect as defined herein

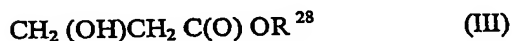
to produce a product comprising a branched (iso) product 2-acetoxy  $(CH_3)_2CH.C(O)OR^{28}$ ,  
 10 wherein  $R^{28}$  is selected from H, or a  $C_1-C_{30}$  alkyl or aryl moiety which may be substituted or unsubstituted and either branched or linear and chemically treating the said branched (iso) product to produce the corresponding lactate or acid of formula II.

By treating or treatment herein is meant carrying out routine chemical treatment such as  
 15 hydrolysis or transesterification reactions on the acetoxy product of the carbonylation suitable to cleave the acetoxy group to produce the hydroxy acid or ester.

The linear (n) and branched (iso) products of the carbonylation may be separated either before or after the treatment step. Preferably, the products of the reaction are separated by  
 20 distillation. The branched and linear products often have widely differing boiling points which makes distillation an effective separation technique for the products of the reaction.

Preferably, the ratio of branched :linear product from the carbonylation process is greater than 1.5:1, more preferably, greater than 2:1, most preferably greater than 2.5:1.  
 25

Accordingly, according to a third aspect of the present invention there is provided a process for the production of 3-hydroxy propanoate ester or acid of formula (III)



30

comprising the steps of :

carbonylating vinyl acetate with carbon monoxide in the presence of a source of hydroxyl groups and of a catalyst system, the catalyst system obtainable by combining:

- 35 (a) a metal of Group VIII B or a compound thereof: and



(b) a bidentate phosphine of general formula (I) in accordance with the first aspect as defined herein

wherein  $R^{28}$  is selected from H, or a  $C_1$ - $C_{30}$  alkyl or aryl moiety which may be substituted or unsubstituted and either branched or linear and carrying out a treatment step on the said linear (n) product 1-acetoxy  $CH_2 \cdot CH_2C(O)OR^{28}$  to produce the 3-hydroxy propanoate ester or acid of formula (III).

The linear (n) and branched (iso) products of the carbonylation may be separated either before or after the treatment step. Preferably, the said products are separated from the reaction products by distillation.

According to a fourth aspect of the present invention there is provided the use of the catalyst system as defined in any of the 1<sup>st</sup> – 3<sup>rd</sup> aspects of the present invention for the production, preferably, industrial production, of a lactate ester or acid of formula (II) the said production comprising the steps of carbonylation of a vinyl acetate followed by treatment of the branched (iso) product of the carbonylation to produce the ester or acid.

According to a fifth aspect of the present invention there is provided the use of the catalyst system as defined in any of the 1<sup>st</sup> – 3<sup>rd</sup> aspects of the present invention for the production, preferably industrial product, of a 3-hydroxy propanoate ester of formula (III) the said production comprising the steps of carbonylation of a vinyl acetate followed by treatment of the linear (n) product of the carbonylation.

Advantageously, the lactate or 3-hydroxy propanoate esters or acids of the present invention may be hydrogenated to produce the 1,2 and 1,3 diols respectively.

Preferably, the treatment is hydrolysis or transesterification and is carried out by any suitable technique known to those skilled in the art. Such techniques are detailed in for example – “Kirkothmer Encyclopaedia of Chemical Technology”, volume 9, 4<sup>th</sup> edition page 783 – “Hydrolysis of Organic Esters”. Such methods include base hydrolysis, acid hydrolysis, steam hydrolysis and enzymic hydrolysis. Preferably, the hydrolysis is base hydrolysis, more preferably, the hydrolysis is carried out in excess base and then acidified to produce the acid product. Hydrogenation of the hydrolysis product may be carried out by any suitable process known to those skilled in the art. Preferably, vapour phase hydrogenation of the hydroxy alkanoate ester is carried out. A suitable technique has been exemplified in WO 01/70659 by

Crabtree et al. Suitable experimental details are set out in examples 1-9 of the published application and illustrate the route to 1,3 propanediol from 3-hydroxy propanoic acid esters. Preferably, the hydrogenation is carried out in a hydrogenation zone containing a heterogenous hydrogenation catalyst. Suitable conditions and catalysts are set out in WO 01/70659, the

5 contents of which are incorporated herein by reference insofar as they relate to the hydrogenation of 3-hydroxy propanoic acid esters. However, for the purposes of the present application such hydrogenation reactions are also deemed applicable to hydrogenation of the lactate ester to produce 1,2 propane diol. Preferably, the transesterification is carried out with the alkanol corresponding to the alkyl group of the alkyl ester product required for example  
10 methanol for converting acetoxy alkyl esters into hydroxy methyl esters and ethanol for converting acetoxy alkyl esters into hydroxy ethyl esters etc. Advantageously, this cleaves the acetoxy group but does not alter the hydroxy alkyl alkanoate. Preferably, the transesterification takes place in the presence of a suitable catalyst such as for example methane sulphonic acid or p-toluene sulphonic acid.

15 Preferably, when K, D, E or Z represent  $-J-Q^3(CR^{13}(R^{14})(R^{15}))CR^{16}(R^{17})(R^{18})$ , the respective K, D, E or Z is on the aryl carbon adjacent the aryl carbon to which A or B is connected or, if not so adjacent, is adjacent a remaining K, D, E or Z group which itself represents  $-J-Q^3(CR^{13}(R^{14})(R^{15}))CR^{16}(R^{17})(R^{18})$ .

20 For ease of reference, any one or more of the five aspects of the invention may be referred to herein as the process of the invention.

Suitably, the process of the invention may be used to catalyse the carbonylation of a vinyl  
25 acetate compound in the presence of carbon monoxide and a hydroxyl group containing compound i.e. the process of the invention may catalyse the conversion of a vinyl acetate compound to the corresponding acetoxy carboxylic acid or ester, respectively, depending on the choice of hydroxyl group containing compound used. Conveniently, the process of the invention may utilise highly stable compounds under typical carbonylation reaction conditions  
30 such that they require little or no replenishment. Conveniently, the process of the invention may have a high rate for the carbonylation reaction of a vinyl acetate compound. Conveniently, the process of the invention may promote high conversion rates of the vinyl acetate compound, thereby yielding the desired product in high yield with little or no impurities. Consequently, the commercial viability of a carbonylation process, such as the

carbonylation of a vinyl acetate compound, may be increased by employing the process of the invention.

The term "Ar" or "aryl" when used herein, includes five-to-ten-membered carbocyclic aromatic or pseudo aromatic groups, such as phenyl, ferrocenyl and naphthyl, which groups are optionally substituted with, in addition to K, D, E or Z, one or more substituents selected from aryl, lower alkyl (which alkyl group may itself be optionally substituted or terminated as defined below), Het, halo, cyano, nitro, OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)OR<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>, C(O)NR<sup>25</sup>R<sup>26</sup>, SR<sup>27</sup>, C(O)SR<sup>27</sup> or C(S)NR<sup>25</sup>R<sup>26</sup> wherein R<sup>19</sup> to R<sup>27</sup> each independently represent hydrogen, aryl or lower alkyl (which alkyl group may itself be optionally substituted or terminated as defined below).

Suitably, when Ar or aryl is cyclopentadienyl and when D and E together with the carbon atoms of the cyclopentadienyl ring to which they are attached form a phenyl ring, the metal M or cation thereof is attached to an indenyl ring system.

By the term "M represents a Group VIB or VIIB metal" in a compound of formula I we include metals such as Cr, Mo, W, Fe, Co, Ni, Ru, Rh, Os, Ir, Pt and Pd. Preferably, the metals are selected from Cr, Mo, W, Fe, Co, Ni, Ru and Rh. For the avoidance of doubt, references to Group VIB or VIIB metals herein should be taken to include Groups 6, 8, 9 and 10 in the modern periodic table nomenclature.

By the term "metal cation thereof" we mean that the Group VIB or VIIB metal (M) in the compound of formula I as defined herein has a positive charge. Suitably, the metal cation may be in the form of a salt or may comprise weakly coordinated anions derived from halo, nitric acid; sulphuric acid; lower alkanolic (up to C<sub>12</sub>) acids such as acetic acid and propionic acid; sulphonic acids such as methane sulphonic acid, chlorosulphonic acid, fluorosulphonic acid, trifluoromethane sulphonic acid, benzene sulphonic acid, naphthalene sulphonic acid, toluene sulphonic acid, e.g. p-toluene sulphonic acid, t-butyl sulphonic acid, and 2-hydroxypropane sulphonic acid; sulphonated ion exchange resins; perhalic acid such as perchloric acid; perfluorinated carboxylic acid such as trichloroacetic acid and trifluoroacetic acid; orthophosphoric acid; phosphonic acid such as benzene phosphonic acid; and acids derived from interactions between Lewis acids and Brønsted acids. Other sources which may provide suitable anions include the tetraphenyl borate derivatives.

Preferably M represents a Group VIB or VIIB metal. In other words the total electron count for the metal M is 18.

- 5 Halo groups, which  $L_2$  may represent and with which the above-mentioned groups may be substituted or terminated, include fluoro, chloro, bromo and iodo.

10 Suitably, if A represents cyclopentadienyl and  $n = 1$ , the compounds of formula I may contain either two cyclopentadienyl rings, two indenyl rings or one indenyl and one cyclopentadienyl ring (each of which ring systems may optionally be substituted as described herein). Such compounds may be referred to as "sandwich compounds" as the metal M or metal cation thereof is sandwiched by the two ring systems. The respective cyclopentadienyl and/or indenyl ring systems may be substantially coplanar with respect to each other or they may be tilted with respect to each other (commonly referred to as bent metallocenes).

- 15 Alternatively, when  $n = 1$ , the compounds of the invention may contain either one cyclopentadienyl or one indenyl ring (each of which ring systems may optionally be substituted as described herein) and one aryl ring (i.e.  $L_1$  represents aryl) which is optionally substituted as defined herein. Suitably, when  $n = 1$  and  $L_1$  represents aryl then the metal M of the compounds of formula I as defined herein is typically in the form of the metal cation.

- 20 Suitably, when  $n = 0$ , the compounds of the invention contain only one cyclopentadienyl or indenyl ring (each of which ring systems may optionally be substituted as described herein). Such compounds may be referred to as "half sandwich compounds". Preferably, when  $n = 0$  then m represents 1 to 5 so that the metal M of the compounds of formula I has an 18 electron count. In other words, when metal M of the compounds of formula I is iron, the total number of electrons contributed by the ligands  $L_2$  is typically five.

30 Suitably, the metal M or metal cation thereof in the cyclopentadienyl compounds of formula I is typically bonded to the cyclopentadienyl ring(s) or the cyclopentadienyl moiety of the indenyl ring(s). Typically, the cyclopentadienyl ring or the cyclopentadienyl moiety of the indenyl ring exhibits a pentahapto bonding mode with the metal; however other bonding modes between the cyclopentadienyl ring or cyclopentadienyl moiety of the indenyl ring and the metal, such as trihapto coordination, are also embraced by the scope of the present invention.

Preferably, in the compound of formula I wherein Ar is cyclopentadienyl, M represents Cr, Mo, Fe, Co or Ru, or a metal cation thereof. Even more preferably, M represents Cr, Fe, Co or Ru or a metal cation thereof. Most preferably, M is selected from a Group VIIIB metal or metal cation thereof. An especially preferred Group VIIIB metal is Fe. Although the metal M  
 5 as defined herein may be in a cationic form, preferably it carries essentially no residual charge due to coordination with  $L_1$  and/or  $L_2$  as defined herein.

Preferably, when  $n = 1$  in the compound of formula I,  $L_1$  represents cyclopentadienyl, indenyl or aryl each of which rings are optionally substituted by one or more substituents selected from  
 10 hydrogen, lower alkyl, halo, cyano,  $OR^{19}$ ,  $OC(O)R^{20}$ ,  $C(O)R^{21}$ ,  $C(O)OR^{22}$ ,  $NR^{23}R^{24}$ ,  $SR^{27}$  or ferrocenyl (by which is meant the cyclopentadienyl, indenyl or aryl ring which  $L_1$  may represent is bonded directly to the cyclopentadienyl ring of the metallocenyl group). More preferably, if the cyclopentadienyl, indenyl or aryl ring which  $L_1$  may represent is substituted it is preferably substituted with one or more substituents selected from  $C_1$ - $C_6$  alkyl, halo, cyano,  
 15  $OR^{19}$ ,  $OC(O)R^{20}$ ,  $C(O)R^{21}$ ,  $C(O)OR^{22}$ ,  $NR^{23}R^{24}$  where  $R^{19}$ ,  $R^{20}$ ,  $R^{21}$ ,  $R^{22}$ ,  $R^{23}$  and  $R^{24}$  each independently represent hydrogen or  $C_1$ - $C_6$  alkyl.

Preferably, when  $n = 1$ ,  $L_1$  represents cyclopentadienyl, indenyl, phenyl or naphthyl optionally substituted as defined herein. Preferably, the cyclopentadienyl, indenyl, phenyl or naphthyl  
 20 groups are unsubstituted. More preferably,  $L_1$  represents cyclopentadienyl, indenyl or phenyl, each of which rings are unsubstituted. Most preferably,  $L_1$  represents unsubstituted cyclopentadienyl.

In a particularly preferred embodiment of the present invention, in a compound of formula I,  $n$   
 25  $= 1$ ,  $L_1$  is as defined herein and  $m = 0$ .

Alternatively, when  $n$  is equal to zero and  $m$  is not equal to zero in a compound of formula I,  $L_2$  represents one or more ligands each of which are independently selected from lower alkyl, halo, CO,  $PR^{43}R^{44}R^{45}$  or  $NR^{46}R^{47}R^{48}$ . More preferably,  $L_2$  represents one or more ligands each  
 30 of which are independently selected from  $C_1$  to  $C_4$  alkyl, halo, particularly chloro, CO,  $PR^{43}R^{44}R^{45}$  or  $NR^{46}R^{47}R^{48}$ , wherein  $R^{43}$  to  $R^{48}$  are independently selected from hydrogen,  $C_1$  to  $C_6$  alkyl or aryl, such as phenyl.

In a particularly preferred alternative embodiment of the present invention, in a compound of  
 35 formula I,  $n = 0$ ,  $L_2$  is as defined herein and  $m = 3$  or 4, particularly 3.

M represents a metal selected from Cr, Mo, Fe, Co or Ru or a metal cation thereof;

$L_1$  represents cyclopentadienyl, indenyl, naphthyl or phenyl, each of which rings may be optionally substituted by one or more substituents selected from  $C_1$ - $C_6$  alkyl, halo, cyano, OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)R<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>;

$L_2$  represents one or more ligands each of which ligands are independently selected from  $C_1$ - $C_6$  alkyl, halo, CO, PR<sup>43</sup>R<sup>44</sup>R<sup>45</sup> or NR<sup>46</sup>R<sup>47</sup>R<sup>48</sup>;

$n = 0$  or  $1$ ;

and  $m = 0$  to  $4$ ;

provided that when  $n = 1$  then  $m = 0$  and when  $m$  does not equal zero then  $n = 0$ .

Further preferred compounds of formula I include those wherein:

15

M represents iron or a cation thereof;

$L_1$  represents cyclopentadienyl, indenyl or phenyl group, each of which groups are optionally substituted by one or more substituents selected from  $C_1$ - $C_6$  alkyl, halo, cyano, OR<sup>19</sup>,

20 OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)R<sup>22</sup>;

$L_2$  represents one or more ligands each of which are independently selected from  $C_1$ - $C_6$  alkyl, halo, CO, PR<sup>43</sup>R<sup>44</sup>R<sup>45</sup> or NR<sup>46</sup>R<sup>47</sup>R<sup>48</sup>, where R<sup>43</sup> to R<sup>48</sup> are independently selected from hydrogen,  $C_1$ - $C_6$  alkyl or phenyl;

25

$n = 0$  or  $1$ ; and  $m = 0$  to  $4$ .

Still further preferred compounds of formula I include those wherein:

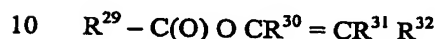
30  $L_1$  represents unsubstituted cyclopentadienyl, indenyl or phenyl, particularly unsubstituted cyclopentadienyl; and,  $n = 1$  and  $m = 0$ .

Alternative preferred compounds of formula I include those wherein:

35  $n = 0$ ;

$L_2$  represents one or more ligands each of which are independently selected from  $C_1$  to  $C_6$  alkyl, halo, CO,  $PR^{43}R^{44}R^{45}$  or  $NR^{46}R^{47}R^{48}$ , where  $R^{43}$  to  $R^{48}$  are independently selected from hydrogen,  $C_1$ - $C_6$  alkyl or phenyl; and  $m = 1$  to 4, particularly 3 or 4. For example, when  $m=3$  the three ligands which  $L_2$  may represent include  $(CO)_2$ halo,  $(PR^{43}R^{44}R^{45})_2$ halo or  
 5  $(NR^{46}R^{47}R^{48})_2$ halo.

References to vinyl acetate herein include references to substituted or unsubstituted vinyl acetate of formula (IV):



wherein  $R^{29}$  may be selected from hydrogen, lower alkyl, aryl, Het, halo, cyano, nitro,  $OR^{19}$ ,  $OC(O)R^{20}$ ,  $C(O)R^{21}$ ,  $C(O)OR^{22}$ ,  $NR^{23}R^{24}$ ,  $C(O)NR^{25}R^{26}$ ,  $C(S)R^{25}R^{26}$ ,  $SR^{27}$ ,  $C(O)SR^{29}$  wherein  $R^{12}$ - $R^{18}$  and  $R^{19}$ - $R^{27}$  are as defined herein.

15

Preferably,  $R^{29}$  is selected from hydrogen, lower alkyl, phenyl or lower alkylphenyl. More preferably, hydrogen, phenyl,  $C_1$ - $C_6$  alkylphenyl or  $C_1$ - $C_6$  alkyl, such as methyl, ethyl, propyl, butyl, pentyl and hexyl, even more preferably,  $C_1$ - $C_6$  alkyl, especially methyl.

20 Preferably,  $R^{30}$ - $R^{32}$  each independently represent hydrogen, lower alkyl, aryl or Het as defined herein. Most preferably,  $R^{30}$ - $R^{32}$  represent hydrogen. As mentioned above,  $R^{28}$  may be optionally substituted, preferably, with one or more substituents selected from lower alkyl, aryl, Het, halo, cyano, nitro,  $OR^{19}$ ,  $OC(O)R^{20}$ ,  $C(O)R^{21}$ ,  $C(O)OR^{22}$ ,  $NR^{23}R^{24}$ ,  $C(O)NR^{25}R^{26}$ ,  $C(S)R^{25}R^{26}$ ,  $SR^{27}$  or  $C(O)SR^{27}$  as defined herein.

25

$R^{28}$  is most preferably the alkyl/aryl group derived from a  $C_1$ - $C_8$  alkanol such as methanol, ethanol, propanol, iso-propanol, iso-butanol, t-butyl alcohol, n-butanol, phenol and chlorocapryl alcohol. The most preferred groups are methyl and ethyl, the most especially preferred group is methyl.

30

The term "Het", when used herein, includes four-to-twelve-membered, preferably four-to-ten-membered ring systems, which rings contain one or more heteroatoms selected from nitrogen, oxygen, sulphur and mixtures thereof, and which rings may contain one or more double bonds or be non-aromatic, partly aromatic or wholly aromatic in character. The ring systems may be  
 35 monocyclic, bicyclic or fused. Each "Het" group identified herein is optionally substituted by

one or more substituents selected from halo, cyano, nitro, oxo, lower alkyl (which alkyl group may itself be optionally substituted or terminated as defined below) OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)OR<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>, C(O)NR<sup>25</sup>R<sup>26</sup>, SR<sup>27</sup>, C(O)SR<sup>27</sup> or C(S)NR<sup>25</sup>R<sup>26</sup> wherein R<sup>19</sup> to R<sup>27</sup> each independently represent hydrogen, aryl or lower alkyl (which alkyl group itself may be optionally substituted or terminated as defined below). The term "Het" thus includes groups such as optionally substituted azetidiny, pyrrolidinyl, imidazolyl, indolyl, furanyl, oxazolyl, isoxazolyl, oxadiazolyl, thiazolyl, thiadiazolyl, triazolyl, oxatriazolyl, thiatriazolyl, pyridazinyl, morpholinyl, pyrimidinyl, pyrazinyl, quinolinyl, isoquinolinyl, piperidinyl, pyrazolyl and piperazinyl. Substitution at Het may be at a carbon atom of the Het ring or, where appropriate, at one or more of the heteroatoms.

"Het" groups may also be in the form of an N oxide.

The term "lower alkyl" when used herein, means C<sub>1</sub> to C<sub>10</sub> alkyl and includes methyl, ethyl, propyl, butyl, pentyl, hexyl and heptyl groups. Unless otherwise specified, alkyl groups may, when there is a sufficient number of carbon atoms, be linear or branched, be saturated or unsaturated, be cyclic, acyclic or part cyclic/acyclic, and/or be substituted or terminated by one or more substituents selected from halo, cyano, nitro, OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)OR<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>, C(O)NR<sup>25</sup>R<sup>26</sup>, SR<sup>27</sup>, C(O)SR<sup>27</sup>, C(S)NR<sup>25</sup>R<sup>26</sup>, aryl or Het, wherein R<sup>19</sup> to R<sup>27</sup> each independently represent hydrogen, aryl or lower alkyl, and/or be interrupted by one or more oxygen or sulphur atoms, or by silano or dialkylsilicon groups.

Lower alkyl groups or alkyl groups which R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, R<sup>4</sup>, R<sup>5</sup>, R<sup>6</sup>, R<sup>7</sup>, R<sup>8</sup>, R<sup>9</sup>, R<sup>10</sup>, R<sup>11</sup>, R<sup>12</sup>, R<sup>13</sup>, R<sup>14</sup>, R<sup>15</sup>, R<sup>16</sup>, R<sup>17</sup>, R<sup>18</sup>, R<sup>19</sup>, R<sup>20</sup>, R<sup>21</sup>, R<sup>22</sup>, R<sup>23</sup>, R<sup>24</sup>, R<sup>25</sup>, R<sup>26</sup>, R<sup>27</sup>, R<sup>28</sup>, R<sup>29</sup>, R<sup>30</sup>, R<sup>31</sup>, R<sup>32</sup>, K, D, E and Z may represent and with which aryl and Het may be substituted, may, when there is a sufficient number of carbon atoms, be linear or branched, be saturated or unsaturated, be cyclic, acyclic or part cyclic/acyclic, and/or be interrupted by one or more of oxygen or sulphur atoms, or by silano or dialkylsilicon groups, and/or be substituted by one or more substituents selected from halo, cyano, nitro, OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)OR<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>, C(O)NR<sup>25</sup>R<sup>26</sup>, SR<sup>27</sup>, C(O)SR<sup>27</sup>, C(S)NR<sup>25</sup>R<sup>26</sup>, aryl or Het wherein R<sup>19</sup> to R<sup>27</sup> each independently represent hydrogen, aryl or lower alkyl.

Similarly, the term "lower alkylene" which A, B and J (when present) represent in a compound of formula I, when used herein, includes C<sub>1</sub> to C<sub>10</sub> groups which can be bonded at two places on the group and is otherwise defined in the same way as "lower alkyl".



Halo groups with which the above-mentioned groups may be substituted or terminated include fluoro, chloro, bromo and iodo.

- 5 Where a compound of a formula herein (eg. formulas I-IV) contains an alkenyl group, cis (E) and trans (Z) isomerism may also occur. The present invention includes the individual stereoisomers of the compounds of any of the formulas defined herein and, where appropriate, the individual tautomeric forms thereof, together with mixtures thereof. Separation of diastereoisomers or cis and trans isomers may be achieved by conventional techniques, e.g. by
- 10 fractional crystallisation, chromatography or H.P.L.C. of a stereoisomeric mixture of a compound one of the formulas or a suitable salt or derivative thereof. An individual enantiomer of a compound of one of the formulas may also be prepared from a corresponding optically pure intermediate or by resolution, such as by H.P.L.C. of the corresponding racemate using a suitable chiral support or by fractional crystallisation of the diastereoisomeric
- 15 salts formed by reaction of the corresponding racemate with a suitable optically active acid or base, as appropriate.

All stereoisomers are included within the scope of the process of the invention.

- 20 It will be appreciated by those skilled in the art that the compounds of formula I (b) may function as ligands that coordinate with the Group VIIIB metal or compound thereof (a) to form the compounds for use in the invention. Typically, the Group VIIIB metal or compound thereof (a) coordinates to the one or more phosphorous, arsenic and/or antimony atoms of the compound of formula I.

- 25 Preferably,  $R^1$  to  $R^{18}$  and  $R^{28}$  each independently represent lower alkyl or aryl. More preferably,  $R^1$  to  $R^{18}$  and  $R^{28}$  each independently represent  $C_1$  to  $C_6$  alkyl,  $C_1$ - $C_6$  alkyl phenyl (wherein the phenyl group is optionally substituted as defined herein) or phenyl (wherein the phenyl group is optionally substituted as defined herein). Even more preferably,  $R^1$  to  $R^{18}$  or
- 30  $R^{28}$  each independently represent  $C_1$  to  $C_6$  alkyl, which is optionally substituted as defined herein. Most preferably,  $R^1$  to  $R^{18}$  or  $R^{28}$  each represent non-substituted  $C_1$  to  $C_6$  alkyl such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl and cyclohexyl.

- Alternatively, or additionally, each of the groups  $R^1$  to  $R^3$ ,  $R^4$  to  $R^6$ ,  $R^7$  to  $R^9$ ,  $R^{10}$  to  $R^{12}$ ,  $R^{13}$  to
- 35  $R^{15}$  or  $R^{16}$  to  $R^{18}$  together independently may form cyclic structures such as 1-norbornyl, 1-

norbornadienyl or adamantyl. Further examples of composite groups include cyclic structures formed between  $R^1 - R^6$  and  $R^7 - R^{12}$ . Alternatively, one or more of the groups may represent a solid phase to which the ligand is attached.

- 5 In a particularly preferred embodiment of the present invention  $R^1, R^4, R^7, R^{10}, R^{13}$  and  $R^{16}$  each represent the same lower alkyl, aryl or Het moiety as defined herein,  $R^2, R^5, R^8, R^{11}, R^{14}$  and  $R^{17}$  each represent the same lower alkyl, aryl or Het moiety as defined herein, and  $R^3, R^6, R^9, R^{12}, R^{15}$  and  $R^{18}$  each represent the same lower alkyl, aryl or Het moiety as defined herein. More preferably  $R^1, R^4, R^7, R^{10}, R^{13}$  and  $R^{16}$  each represent the same  $C_1-C_6$  alkyl, particularly
- 10 non-substituted  $C_1-C_6$  alkyl, such as methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl or cyclohexyl;  $R^2, R^5, R^8, R^{11}, R^{14}$  and  $R^{17}$  each independently represent the same  $C_1-C_6$  alkyl as defined above; and  $R^3, R^6, R^9, R^{12}, R^{15}$  and  $R^{18}$  each independently represent the same  $C_1-C_6$  alkyl as defined above. For example:  $R^1, R^4, R^7, R^{10}, R^{13}$  and  $R^{16}$  each represent methyl;  $R^2, R^5, R^8, R^{11}, R^{14}$  and  $R^{17}$  each represent ethyl; and,  $R^3, R^6, R^9, R^{12}, R^{15}$  and  $R^{18}$  each represent n-butyl or n-pentyl.
- 15

- In an especially preferred embodiment of the present invention each  $R^1$  to  $R^{18}$  and  $R^{28}$  group represents the same lower alkyl, aryl, or Het moiety as defined herein. Preferably, each  $R^1$  to  $R^{18}$  represents the same  $C_1$  to  $C_6$  alkyl group, particularly non-substituted  $C_1-C_6$  alkyl, such as
- 20 methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, tert-butyl, pentyl, hexyl and cyclohexyl. Most preferably, each  $R^1$  to  $R^{18}$  and  $R^{28}$  represents methyl.

- In the compound of formula I, preferably each  $Q^1, Q^2$  and  $Q^3$  (when present) are the same. Most preferably, each  $Q^1, Q^2$  and  $Q^3$  (when present) represents phosphorous.

- 25 Preferably, in the compound of formula I, A, B and J (when present) each independently represent  $C_1$  to  $C_6$  alkylene which is optionally substituted as defined herein, for example with lower alkyl groups. Preferably, the lower alkylene groups which A, B and J (when present) represent are non-substituted. A particular preferred lower alkylene which A, B and J may
- 30 independently represent is  $-CH_2-$  or  $-C_2H_4-$ . Most preferably, each of A, B and J (when present) represent the same lower alkylene as defined herein, particularly  $-CH_2-$ .

- Preferably, in the compound of formula I when K, D, E or Z does not represent -J-  $Q^3(CR^{13}(R^{14})(R^{15}))CR^{16}(R^{17})(R^{18})$ , K, D, E or Z represents hydrogen, lower alkyl, phenyl or
- 35 lower alkylphenyl. More preferably, K, D, E or Z represent hydrogen, phenyl,  $C_1-C_6$

alkylphenyl or C<sub>1</sub>-C<sub>6</sub> alkyl, such as methyl, ethyl, propyl, butyl, pentyl and hexyl. Most preferably, K, D, E or Z represents hydrogen.

5 Preferably, in the compound of formula I when K, D, E and Z together with the carbon atoms of the aryl ring to which they are attached do not form a phenyl ring, K, D, E and Z each independently represent hydrogen, lower alkyl, phenyl or lower alkylphenyl. More preferably, K, D, E and Z each independently represent hydrogen, phenyl, C<sub>1</sub>-C<sub>6</sub> alkylphenyl or C<sub>1</sub>-C<sub>6</sub> alkyl, such as methyl, ethyl, propyl, butyl, pentyl and hexyl. Even more preferably, K, D, E and Z represent the same substituent. Most preferably, they represent hydrogen.

10 Preferably, in the compound of formula I when K, D, E or Z does not represent -J-Q<sup>3</sup>(CR<sup>13</sup>(R<sup>14</sup>)(R<sup>15</sup>))CR<sup>16</sup>(R<sup>17</sup>)(R<sup>18</sup>) and K, D, E and Z together with the carbon atoms of the aryl ring to which they are attached do not form a phenyl ring, each of K, D, E and Z represent the same group selected from hydrogen, lower alkyl, aryl, or Het as defined herein; particularly  
15 hydrogen or C<sub>1</sub>-C<sub>6</sub> alkyl (more particularly unsubstituted C<sub>1</sub>-C<sub>6</sub> alkyl), especially hydrogen.

20 Preferably, in the compound of formula I when two of K, D, E and Z together with the carbon atoms of the aryl ring to which they are attached form a phenyl ring, then the phenyl ring is optionally substituted with one or more substituents selected from aryl, lower alkyl (which alkyl group may itself be optionally substituted or terminated as defined below), Het, halo, cyano, nitro, OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)OR<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>, C(O)NR<sup>25</sup>R<sup>26</sup>, SR<sup>27</sup>, C(O)SR<sup>27</sup> or C(S)NR<sup>25</sup>R<sup>26</sup> wherein R<sup>19</sup> to R<sup>27</sup> each independently represent hydrogen or lower alkyl (which alkyl group may itself be optionally substituted or terminated as defined herein). More  
25 preferably, the phenyl ring is not substituted by any substituents i.e. it bears hydrogen atoms only.

Preferred compounds of formula I include those wherein:

30 A and B each independently represent unsubstituted C<sub>1</sub> to C<sub>6</sub> alkylene;

K, D, Z and E each independently represent hydrogen, C<sub>1</sub>-C<sub>6</sub> alkyl, phenyl, C<sub>1</sub>-C<sub>6</sub> alkylphenyl or -J-Q<sup>3</sup>(CR<sup>13</sup>(R<sup>14</sup>)(R<sup>15</sup>))CR<sup>16</sup>(R<sup>17</sup>)(R<sup>18</sup>) where J represents unsubstituted C<sub>1</sub> to C<sub>6</sub> alkylene; or two of K, D, Z and E together with the carbon atoms of the aryl ring to which they are attached form a phenyl ring which is optionally substituted by one or more substituents selected from  
35 lower alkyl, phenyl or lower alkylphenyl.

$R^1$  to  $R^{18}$  each independently represent  $C_1$  to  $C_6$  alkyl, phenyl or  $C_1$  to  $C_6$  alkylphenyl.

Further preferred compounds of formula I include those wherein:

5

A and B both represent  $-\text{CH}_2-$  or  $\text{C}_2\text{H}_4$ , particularly  $\text{CH}_2$ ;

10 K, D, Z and E each independently represent hydrogen,  $C_1$ - $C_6$  alkyl phenyl or  $C_1$ - $C_6$  alkyl or  $-J-Q^3(\text{CR}^{13}(\text{R}^{14})(\text{R}^{15}))\text{CR}^{16}(\text{R}^{17})(\text{R}^{18})$  where J is the same as A; or two of K, D, E and Z together with the carbon atoms of the aryl ring to which they are attached form an unsubstituted phenyl ring;

$R^1$  to  $R^{18}$  each independently represent  $C_1$  to  $C_6$  alkyl;

15 Still further preferred compounds of formula I include those wherein:

$R^1$  to  $R^{18}$  are the same and each represents  $C_1$  to  $C_6$  alkyl, particularly methyl.

Still further preferred compounds of formula I include those wherein:

20

K, D, Z and E are each independently selected from the group consisting of hydrogen or  $C_1$  to  $C_6$  alkyl, particularly where each of K, D, Z and E represent the same group, especially where each of K, D, Z and E represent hydrogen; or

25 K represents  $-\text{CH}_2-Q^3(\text{CR}^{13}(\text{R}^{14})(\text{R}^{15}))\text{CR}^{16}(\text{R}^{17})(\text{R}^{18})$  and D, Z and E are each independently selected from the group consisting of hydrogen or  $C_1$  to  $C_6$  alkyl, particularly where both D and E represent the same group, especially where D, Z and E represent hydrogen.

Especially preferred specific compounds of formula I include those wherein:

30

each  $R^1$  to  $R^{12}$  is the same and represents methyl;

A and B are the same and represent  $-\text{CH}_2-$ ;

K, D, Z and E are the same and represent hydrogen.

The present invention provides a process for the carbonylation of a vinyl acetate compound comprising contacting a vinyl acetate compound with carbon monoxide and a hydroxyl group containing compound in the presence of a catalyst compound as defined in the present invention.

5

Suitably, the hydroxyl group containing compound includes water or an organic molecule having a hydroxyl functional group. Preferably, the organic molecule having a hydroxyl functional group may be branched or linear, and comprises an alkanol, particularly a C<sub>1</sub>-C<sub>30</sub> alkanol, including aryl alkanols, which may be optionally substituted with one or more substituents selected from lower alkyl, aryl, Het, halo, cyano, nitro, OR<sup>19</sup>, OC(O)R<sup>20</sup>, C(O)R<sup>21</sup>, C(O)OR<sup>22</sup>, NR<sup>23</sup>R<sup>24</sup>, C(O)NR<sup>25</sup>R<sup>26</sup>, C(S)R<sup>25</sup>R<sup>26</sup>, SR<sup>27</sup> or C(O)SR<sup>27</sup> as defined herein. Highly preferred alkanols are C<sub>1</sub>-C<sub>8</sub> alkanols such as methanol, ethanol, propanol, iso-propanol, isobutanol, t-butyl alcohol, n-butanol, phenol and chlorocapryl alcohol. Although the monoalkanols are most preferred, poly-alkanols, preferably, selected from di-ols such as diols, triols, tetra-ols and sugars may also be utilised. Typically, such polyalkanols are selected from 1, 2-ethanediol, 1,3-propanediol, glycerol, 1,2,4 butanetriol, 2-(hydroxymethyl)-1,3-propanediol, 1,2,6 trihydroxyhexane, pentaerythritol, 1,1,1 tri(hydroxymethyl)ethane, nannose, sorbose, galactose and other sugars. Preferred sugars include sucrose, fructose and glucose. Especially preferred alkanols are methanol and ethanol. The most preferred alkanol is methanol.

20

The amount of alcohol is not critical. Generally, amounts are used in excess of the amount of vinyl acetate compound to be carbonylated. Thus the alcohol may serve as the reaction solvent as well, although, if desired, separate solvents may also be used.

25

It will be appreciated that the end product of the reaction is determined at least in part by the source of hydroxyl group containing compound used. If water is used as the hydroxyl group containing compound then the end product is the corresponding carboxylic acid, whereas use of an alkanol produces the corresponding ester. Use of methanol conveniently produces the 2-acetoxy methyl propanoate or 3-acetoxymethyl propanoate.

30

In the process according to the present invention, the carbon monoxide may be used in pure form or diluted with an inert gas such as nitrogen, carbon dioxide or a noble gas such as argon. Small amounts of hydrogen, typically less than 5% by volume, may also be present.

35

The ratio (volume/volume) of vinyl acetate compound to hydroxyl group containing compound may vary between wide limits and suitably lies in the range of 1:0.1 to 1:10, preferably from between 2:1 to 1:2 and up to a large excess of hydroxyl group containing compounds when the latter is also the reaction solvent such as up to a 50:1 excess of hydroxyl group containing compounds.

The amount of the catalyst of the invention used in the carbonylation process of the vinyl acetate compound is not critical. Good results may be obtained when, preferably, the amount of Group VIII metal is in the range  $10^{-7}$  to  $10^{-1}$  moles per mole of vinyl acetate compound, more preferably,  $10^{-6}$  to  $10^{-2}$  moles, most preferably  $10^{-5}$  to  $10^{-2}$  moles per mole of ethylenically unsaturated compound. Preferably, the amount of bidentate compound of formula I to unsaturated compound is in the range  $10^{-7}$  to  $10^{-1}$ , more preferably,  $10^{-6}$  to  $10^{-2}$ , most preferably,  $10^{-5}$  to  $10^{-2}$  moles per mole of vinyl acetate compound.

Suitably, although non-essential to the invention, the carbonylation of a vinyl acetate compound as defined herein may be performed in one or more aprotic solvents. Suitable solvents include ketones, such as for example methylbutylketone; ethers, such as for example anisole (methyl phenyl ether), 2,5,8-trioxanonane (diglyme), diethyl ether, dimethyl ether, tetrahydrofuran, diphenylether, diisopropylether and the dimethylether of di-ethylene-glycol; esters, such as for example methylacetate, dimethyladipate methyl benzoate, dimethyl phthalate and butyrolactone; amides, such as for example dimethylacetamide, N-methylpyrrolidone and dimethyl formamide; sulfoxides and sulphones, such as for example dimethylsulphoxide, di-isopropylsulphone, sulfolane (tetrahydrothiophene-2,2-dioxide), 2-methylsulfolane, diethyl sulphone, tetrahydrothiophene 1,1-dioxide and 2-methyl-4-ethylsulfolane; aromatic compounds, including halo variants of such compounds eg. benzene, toluene, ethyl benzene o-xylene, m-xylene, p-xylene, chlorobenzene, o-dichlorobenzene, m-dichlorobenzene; alkanes, including halo variants of such compounds eg. hexane, heptane, 2,2,3-trimethylpentane, methylene chloride and carbon tetrachloride; nitriles eg. benzonitrile and acetonitrile.

Very suitable are aprotic solvents having a dielectric constant that is below a value of 50, more preferably in the range of 3 to 8, at 298.15 K and  $1 \times 10^5 \text{ Nm}^{-2}$ . In the present context, the dielectric constant for a given solvent is used in its normal meaning of representing the ratio of the capacity of a condenser with that substance as dielectric to the capacity of the same condenser with a vacuum for dielectric. Values for the dielectric constants of common organic

liquids can be found in general reference books, such as the Handbook of Chemistry and Physics, 76<sup>th</sup> edition, edited by David R. Lide et al, and published by CRC press in 1995, and are usually quoted for a temperature of about 20°C or 25°C, i.e. about 293.15k or 298.15 K, and atmospheric pressure, i.e. about  $1 \times 10^5 \text{ Nm}^{-2}$ , or can readily be converted to that  
5 temperature and pressure using the conversion factors quoted. If no literature data for a particular compound is available, the dielectric constant may be readily measured using established physico-chemical methods.

For example, the dielectric constant of anisole is 4.3 (at 294.2 K), of diethyl ether is 4.3 (at  
10 293.2 K), of sulfolane is 43.4 (at 303.2 K), of methylpentanoate is 5.0 (at 293.2 K), of diphenylether is 3.7 (at 283.2 K), of dimethyladipate is 6.8 (at 293.2 K), of tetrahydrofuran is 7.5 (at 295.2 K), of methylnonanoate is 3.9 (at 293.2 K). A preferred solvent is anisole.

If the hydroxyl group containing compound is an alkanol, an aprotic solvent will be generated  
15 by the reaction as the ester carbonylation product of the vinyl acetate compound, carbon monoxide and the alkanol is an aprotic solvent.

The process may be carried out in an excess of aprotic solvent, i.e. at a ratio (v/v) of aprotic solvent to hydroxyl group containing compound of at least 1:1. Preferably, this ratio ranges  
20 from 1:1 to 10:1 and more preferably from 1:1 to 5:1. Most preferably the ratio (v/v) ranges from 1.5:1 to 3:1.

Despite the foregoing it is preferred that the reaction is carried out in the absence of any external added aprotic solvent ie. an aprotic solvent not generated by the reaction itself.  
25

The catalyst compounds of the present invention may act as a "heterogeneous" catalyst or a "homogeneous" catalyst.

By the term "homogeneous" catalyst we mean a catalyst, i.e. a compound of the invention,  
30 which is not supported but is simply admixed or formed in-situ with the reactants of the carbonylation reaction (e.g. the vinyl acetate compound, the hydroxyl containing compound and carbon monoxide), preferably in a suitable solvent as described herein.

By the term "heterogeneous" catalyst we mean a catalyst, i.e. the compound of the invention,  
35 which is carried on a support.

Thus according to a further aspect, the present invention provides a process for the carbonylation of vinyl acetate compounds as defined herein wherein the process is carried out with the catalyst comprising a support, preferably an insoluble support.

5

Preferably, the support comprises a polymer such as a polyolefin, polystyrene or polystyrene copolymer such as a divinylbenzene copolymer or other suitable polymers or copolymers known to those skilled in the art; a silicon derivative such as a functionalised silica, a silicone or a silicone rubber; or other porous particulate material such as for example inorganic oxides and inorganic chlorides.

10

Preferably the support material is porous silica which has a surface area in the range of from 10 to 700 m<sup>2</sup>/g, a total pore volume in the range of from 0.1 to 4.0 cc/g and an average particle size in the range of from 10 to 500 μm. More preferably, the surface area is in the range of from 50 to 500 m<sup>2</sup>/g, the pore volume is in the range of from 0.5 to 2.5 cc/g and the average particle size is in the range of from 20 to 200 μm. Most desirably the surface area is in the range of from 100 to 400 m<sup>2</sup>/g, the pore volume is in the range of from 0.8 to 3.0 cc/g and the average particle size is in the range of from 30 to 100 μm. The average pore size of typical porous support materials is in the range of from 10 to 1000 . Preferably, a support material is used that has an average pore diameter of from 50 to 500 , and most desirably from 75 to 350 . It may be particularly desirable to dehydrate the silica at a temperature of from 100°C to 800°C anywhere from 3 to 24 hours.

15

20

Suitably, the support may be flexible or a rigid support, the insoluble support is coated and/or impregnated with the compounds of the process of the invention by techniques well known to those skilled in the art.

25

Alternatively, the compounds of the process of the invention are fixed to the surface of an insoluble support, optionally via a covalent bond, and the arrangement optionally includes a bifunctional spacer molecule to space the compound from the insoluble support.

30

The compounds of the invention may be fixed to the surface of the insoluble support by promoting reaction of a functional group present in the compound of formula I, for example a substituent K, D, Z and E of the aryl moiety, with a complimentary reactive group present on or previously inserted into the support. The combination of the reactive group of the support

35



with a complimentary substituent of the compound of the invention provides a heterogeneous catalyst where the compound of the invention and the support are linked via a linkage such as an ether, ester, amide, amine, urea, keto group.

- 5 The choice of reaction conditions to link a compound of the process of the present invention to the support depend upon the vinyl acetate compound and the groups of the support. For example, reagents such as carbodiimides, 1,1'-carbonyldiimidazole, and processes such as the use of mixed anhydrides, reductive amination may be employed.
- 10 According to a further aspect, the present invention provides the use of the process of any aspect of the invention wherein the catalyst is attached to a support.

- Particularly preferred is when the organic groups  $R^1, R^2, R^3, R^4, R^5, R^6, R^7, R^8, R^9, R^{10}, R^{11}$  and  $R^{12}$  or  $R^1 - R^{18}$  when associated with their respective carbon atom form composite groups
- 15 which are at least as sterically hindering as t-butyl. Steric hindrance in this context is as discussed at page 14 et seq of "Homogenous Transition Metal Catalysis - A Gentle Art", by C Masters, published by Chapman and Hall 1981. These steric groups may be cyclic, part-cyclic or acyclic. When cyclic or part cyclic, the group may be substituted or unsubstituted or be saturated or unsaturated. The cyclic or part cyclic groups may contain, including the tertiary
- 20 carbon atom, from  $C_4 - C_{30}$ , more preferably  $C_6 - C_{20}$ , most preferably  $C_{10} - C_{15}$  carbon atoms in the cyclic structure. The cyclic structure may be substituted by one or more substituents selected from halo, cyano, nitro,  $OR^{19}$ ,  $OC(O)R^{20}$ ,  $C(O)R^{21}$ ,  $C(O)OR^{22}$ ,  $NR^{23}R^{24}$ ,  $C(O)NR^{25}R^{26}$ ,  $SR^{27}$ ,  $C(O)SR^{27}$ ,  $C(S)NR^{25}R^{26}$ , aryl or Het, wherein  $R^{19}$  to  $R^{27}$  each independently represent hydrogen, aryl or lower alkyl, and/or be interrupted by one or more
- 25 oxygen or sulphur atoms, or by silano or dialkylsilcon groups.

- The bridging group Ar is an aryl moiety, eg. a phenyl group, which may be optionally substituted, provided that the two phosphorus atoms are linked to adjacent carbon atoms, eg. at the 1 and 2 positions on the phenyl group. Furthermore, the aryl moiety may be a fused
- 30 polycyclic group eg. naphthalene, biphenylene or indene.

- Examples of suitable bidentate ligands are bis (di-t-butyl phosphino)-o-xylene (also known as 1,2 bis (di-t-butylphosphinomethyl) benzene); 1,2 bis (diadamantylphosphinomethyl) benzene; 1,2 bis (diadamantylphosphinomethyl) naphthalene; 1,2 bis (di-t-pentyl phosphino)-o-xylene
- 35 (also known as 1,2 bis (di-t-pentyl-phosphinomethyl) benzene); and bis 1,2 (di-t-butyl

phosphino) naphthalene. Additionally, the bidentate phosphine may be bonded to a suitable polymeric substrate via at least one of the bridging group Ar, the linking group A or the linking group B eg. bis (di-t-butyl phosphino)-o-xylene may be bonded via the xylene group to polystyrene to give an immobile heterogeneous catalyst. Examples of suitable bidentate

5 ferrocene ligands are

- 1,2-bis-(ditertbutylphosphinomethyl) ferrocene;
- 1,2,3-tris-(ditertbutylphosphinomethyl) ferrocene;
- 1,2 bis (diadamantylphosphinomethyl) ferrocene; and
- 1,2 bis (di-t-pentyl phosphinomethyl) ferrocene.

10

The amount of bidentate ligand used can vary within wide limits. Preferably, the bidentate ligand is present in an amount such that the ratio of the number of moles of the bidentate ligand present to the number of moles of the Group VIII metal present is from 1 to 50 eg. 1 to 10 and particularly from 1 to 5 mol per mol of metal. More preferably, the mol:mol range of compounds of formula I to Group VIIIB metal is in the range of 1:1 to 3:1, most preferably in the range of 1:1 to 1.25:1. Conveniently, the possibility of applying these low molar ratios is advantageous, as it avoids the use of an excess of the compound of formula I and hence minimises the consumption of these usually expensive compounds. Suitably, the catalysts of the invention are prepared in a separate step preceding their use in-situ in the carbonylation reaction of a vinyl acetate compound.

20

Conveniently, the process of the invention may be carried out by dissolving the Group VIIIB metal or compound thereof as defined herein in a suitable solvent such as one of the hydroxyl group containing compounds or aprotic solvents previously described (a particularly preferred solvent would be the ester or acid product of the specific carbonylation reaction eg. Methyl lactate for vinyl acetate carbonylation) and subsequently admixing with a compound of formula I as defined herein.

25

The carbon monoxide may be used in the presence of other gases which are inert in the reaction. Examples of such gases include hydrogen, nitrogen, carbon dioxide and the noble gases such as argon.

30

Suitable Group VIIIB metals or a compound thereof which may be combined with a compound of formula I include cobalt, nickel, palladium, rhodium and platinum. Preferably, the Group VIIIB metal is palladium or a compound thereof. Suitable compounds of such

35

Group VIII metals include salts of such metals with, or compounds comprising weakly coordinated anions derived from, nitric acid; sulphuric acid; lower alkanolic (up to C<sub>12</sub>) acids such as acetic acid and propionic acid; sulphonic acids such as methane sulphonic acid, chlorosulphonic acid, fluorosulphonic acid, trifluoromethane sulphonic acid, benzene sulphonic acid, naphthalene sulphonic acid, toluene sulphonic acid; e.g. p-toluene sulphonic acid, t-butyl sulphonic acid, and 2-hydroxypropane sulphonic acid; sulphonated ion exchange resins; perhalic acid such as perchloric acid; ; halogenated carboxylic acids such as trichloroacetic acid and trifluoroacetic acid; orthophosphoric acid; phosphonic acids such as benzenephosphonic acid; and acids derived from interactions between Lewis acids and

10 Broensted acids. Other sources which may provide suitable anions include the optionally halogenated tetraphenyl borate derivatives, e.g. perfluorotetraphenyl borate. Additionally, zero valent palladium complexes particularly those with labile ligands, e.g. triphenylphosphine or alkenes such as dibenzylideneacetone or styrene or tri(dibenzylideneacetone)dipalladium may be used.

15 The anion may be derived from or introduced as one or more of an acid having a pK<sub>a</sub> measured in aqueous solution at 18°C of less than 4, more preferably, less than 3, a salt with a cation that does not interfere with the reaction, e.g. metal salts or largely organic salts such as alkyl ammonium, and a precursor, such as an ester, that can break down under reaction

20 conditions to generate the anion in situ. Suitable acids and salts include the acids and salts, other than unsubstituted carboxylates, listed supra.

The quantity of anion present is not critical to the catalytic behaviour of the catalyst system. The molar ratio of anion to palladium may be from 1:1 to 500:1, preferably from 2:1 to 100:1

25 and particularly from 3:1 to 30:1. Where the anion is provided by a combination of acid and salt, the relative proportion of the acid and salt is not critical. As mentioned, the catalyst system of the present invention may be used homogeneously or heterogeneously. Preferably, the catalyst system is used homogeneously.

30 The catalyst system of the present invention is preferably constituted in the liquid phase which may be formed by one or more of the reactants or by the use of a suitable solvent.

The molar ratio of the amount of vinyl acetate compound used in the reaction to the amount of hydroxyl providing compound is not critical and may vary between wide limits, eg. from

35 0.001:1 to 100:1 mol/mol.

The product of the reaction may be separated from the other components by any suitable means. However, it is an advantage of the present process that significantly fewer by-products are formed thereby reducing the need for further purification after the initial separation of the product as may be evidenced by the generally significantly higher selectivity. A further advantage is that the other components which contain the catalyst system which may be recycled and/or reused in further reactions with minimal supplementation of fresh catalyst.

Preferably, the carbonylation is carried out at a temperature of between  $-10$  to  $150^{\circ}\text{C}$ , more preferably  $0^{\circ}\text{C}$  to  $140^{\circ}\text{C}$ , most preferably  $20^{\circ}\text{C}$  to  $120^{\circ}\text{C}$ . An especially preferred temperature is one chosen between  $80^{\circ}\text{C}$  to  $120^{\circ}\text{C}$ . Advantageously, the carbonylation can be carried out at moderate temperatures, it is particularly advantageous to be able to carry out the reaction at room temperature ( $20^{\circ}\text{C}$ ).

Preferably, when operating a low temperature carbonylation, the carbonylation is carried out between  $-30^{\circ}\text{C}$  to  $49^{\circ}\text{C}$ , more preferably,  $-10^{\circ}\text{C}$  to  $45^{\circ}\text{C}$ , still more preferably  $0^{\circ}\text{C}$  to  $45^{\circ}\text{C}$ , most preferably  $10^{\circ}\text{C}$  to  $45^{\circ}\text{C}$ . Especially preferred is a range of  $10$  to  $35^{\circ}\text{C}$ .

Preferably, the carbonylation is carried out at a CO partial pressure of between  $0.80 \times 10^5 \text{ N.m}^{-2}$  to  $90 \times 10^5 \text{ N.m}^{-2}$ , more preferably  $1 \times 10^5 \text{ N.m}^{-2}$  to  $65 \times 10^5 \text{ N.m}^{-2}$ , most preferably  $1$  to  $30 \times 10^5 \text{ N.m}^{-2}$ . Especially preferred is a CO partial pressure of  $5$  to  $20 \times 10^5 \text{ N.m}^{-2}$ .

Preferably, a low pressure carbonylation is also envisaged. Preferably, when operating a low pressure carbonylation the carbonylation is carried out at a CO partial pressure of between  $0.1$  to  $5 \times 10^5 \text{ N.m}^{-2}$ , more preferably  $0.2$  to  $2 \times 10^5 \text{ N.m}^{-2}$ , most preferably  $0.5$  to  $1.5 \times 10^5 \text{ N.m}^{-2}$ .

As mentioned above, vinyl acetate can be substituted or non-substituted. However, it is preferred that the vinyl acetate is unsubstituted.

The following examples further illustrate the present invention.

#### Preparation of 1,2-bis-(ditertbutylphosphinomethyl) benzene

The preparation of this ligand was carried out in the manner disclosed in WO 99/47528 in accordance with example 18.

**Preparation of 1,2-bis-(ditertbutylphosphinomethyl)ferrocene**

5 Di-tertbutylphosphine (Aldrich, 0.616 ml, 3.33 mmol) was added to a solution of 1,2-bis(dimethylaminomethyl)ferrocene (Example 1, 0.5 g, 1.66 mmol) in anhydrous acetic acid (100 ml) under nitrogen and the resulting mixture is stirred at 80°C for 72 hours. The anhydrous acetic acid is removed *in vacuo* at approximately 70°C to yield the crude title product as an orange/yellow solid. The crude product is recrystallised from ethanol with  
10 cooling to -17°C, filtered and the filtrate washed with cold ethanol to yield the title compound as a pale yellow solid (0.365 g, 44%, 84°C).

<sup>1</sup>H NMR (250 MHz; CDCl<sub>3</sub>): δ4.4 (2H, d, J = 2Hz); 3.95(5H, s); 3.75 (1H, t, 2Hz); 2.8 (2H, dd, 12Hz, 2Hz); 2.6 (2H, dd, 12Hz, 2Hz); 1.1 (18H, m).

15 <sup>13</sup>C NMR (63 MHz; CDCl<sub>3</sub>): δ86.73 (d, 5.46 Hz); 70.08 (d, 4.41 Hz); 69.4665(s); 63.75(s); 31.80 (d, 2Hz); 31.45 (d, 1.98Hz); 29.89 (d, 1.88 Hz).

<sup>31</sup>P NMR (101 MHz; CDCl<sub>3</sub>): δ15.00 ppm.

20 Elemental analysis: Found: C:66.79%; H:9.57%  
Calculated: C:66.93%; H:9.63%

**Preparation of 1,2 bis(diadamantylphosphinomethyl) benzene**

25 The preparation of this ligand was carried out as follows.

**1.1 Preparation of (1-Ad)<sub>2</sub>P(O)Cl**

30 Phosphorous trichloride (83 cm<sup>3</sup>, 0.98 mol) was added rapidly via cannula to a combination of aluminium chloride (25.0 g, 0.19 mol) and adamantane (27.2 g, 0.20 mol) affording a tan suspension. The reaction was heated to reflux. After 10 mins, a yellow-orange suspension was formed (colour due to P(O)Cl<sub>3</sub>?). The reaction was refluxed for a total of 6 h. The excess PCl<sub>3</sub> was removed by distillation at atmospheric pressure (BP 75 °C). On cooling to ambient  
35 temperature, an orange solid was formed. Chloroform (250 cm<sup>3</sup>) was added yielding an orange

suspension, which was cooled to 0 °C. Water (150 cm<sup>3</sup>) was added slowly: initially the suspension viscosity increased, but on full addition of water the viscosity lessened. From this point the reaction was no longer kept under an atmosphere of Ar. The suspension was Buchner filtered to remove the yellow-orange solid impurity. The filtrate consisted of a two phase system. The lower phase was separated using a separating funnel, dried over MgSO<sub>4</sub> and Buchner filtered. The volatiles were removed via rotary evaporation, drying finally *in-vacuo*, affording an off-white powder. Yield 35.0 g, 99 %. <sup>31</sup>P NMR:  $\delta$  = 85 ppm, 99 % pure. FW = 352.85.

## 1.2 Preparation of (1-Ad)<sub>2</sub>PH

LiAlH<sub>4</sub> (2.54 g, 67.0 mmol) was added over 90 minutes to a chilled (-10 °C) solution of (1-Ad)<sub>2</sub>P(O)Cl (10.00 g, 28.3 mmol) in THF. (120 cm<sup>3</sup>). The reaction was allowed to warm to ambient temperature then stirred for 20 h. The grey suspension was cooled to -10 °C. HCl (aq., 5 cm<sup>3</sup> c. HCl in 50 cm<sup>3</sup> degassed water) was added slowly via syringe (initially very slowly due to exotherm of reaction), yielding a two phase system, with some solid material in the lower phase. Further HCl (~ 5 cm<sup>3</sup> c. HCl) was added to improve the separation of the layers. The upper phase was removed via flat ended cannula, dried over MgSO<sub>4</sub> and filtered via cannula. The volatiles were removed *in-vacuo* affording the product as a white powder, isolated in the glovebox. Yield 6.00 g, 70 %. <sup>31</sup>P NMR:  $\delta$  = 17 ppm, 100 % pure. FW = 302.44.

## 1.3 Preparation of (1-Ad)<sub>2</sub>PCl

A solution of Ad<sub>2</sub>PH (10.5 g, 34.7 mmol) and DBU (6.12 cm<sup>3</sup>, 40.9 mmol) in toluene (250 cm<sup>3</sup>) was chilled to -10 °C. Phosgene solution (30.0 cm<sup>3</sup>, 56.7 mmol, was added slowly via cannula, transferring via a measuring cylinder. This afforded a highly viscous pale yellow suspension. Additional toluene (100 cm<sup>3</sup>) was added via cannula to lessen the viscosity and ease the stirring. The reaction was filtered via cannula affording a yellow filtrate. The residue was washed with additional toluene (2 × 100 cm<sup>3</sup>) and the washings combined with the original filtrate. The volatiles were removed *in-vacuo* affording a pale yellow solid, which was washed with pentane (2 × 30 cm<sup>3</sup>, washings practically colourless). The product was dried *in-vacuo* and isolated in the glovebox as a lemon yellow powder. Yield 7.84 g, 67 %. <sup>31</sup>P NMR:  $\delta$  = 139 ppm, 99+ % pure. FW = 336.88.

#### 1.4 Preparation of 1,2-bis(di-1-adamantylphosphinomethyl)benzene

##### 1.4.1 Preparation of DI-SODIO-ORTHO-XYLENE(DISOD)

- 5 Bu<sup>n</sup>Li (2.5 M in hexanes, 11.28 cm<sup>3</sup>, 28.2 mmol) was added dropwise via syringe over 15 minutes to a stirred suspension of NaOBu<sup>t</sup> (crushed, 2.71 g, 28.2 mmol), *o*-xylene (1.15 cm<sup>3</sup>, 9.4 mmol) and N,N,N',N' – tetramethyl ethylene diamine (TMEDA) (4.26 cm<sup>3</sup>, 28.2 mmol) in heptane (100 cm<sup>3</sup>). The reaction was heated at 60 °C for 2 h, then allowed to cool / settle, affording a bright orange solid (DISOD) and pale yellow solution. The solution was removed  
10 via cannula filtration and the solid washed with additional heptane (50 cm<sup>3</sup>) and dried *in-vacuo*. 90 % yield assumed, 8.47 mmol.

##### 1.4.2 Reaction of DI-SODIO-ORTHO-XYLENE with 2 equiv (1-Ad)<sub>2</sub>PCl

- 15 A suspension of DISOD (8.47 mmol) in Et<sub>2</sub>O (100 cm<sup>3</sup>) was prepared at -78 °C. A suspension of Ad<sub>2</sub>PCl (5.70 g, 16.9 mmol) in Et<sub>2</sub>O (120 cm<sup>3</sup>) was stirred rapidly at -78 °C and added via wide-bore cannula to the DISOD suspension. The reaction was allowed to warm to ambient temperature and stirred for 18 h, affording a pale yellow turbid solution. Water (degassed, 100 cm<sup>3</sup>) added via cannula affording a two phase system, with a great deal of white solid present  
20 (product) due to the low solubility of this material. The upper phase (Et<sub>2</sub>O) was removed via cannula. The solid in the aqueous phase was extracted using dichloromethane (200 cm<sup>3</sup>), forming two clear phases. The lower phase (CH<sub>2</sub>Cl<sub>2</sub>) was removed via cannula and combined with the original Et<sub>2</sub>O phase. The volatiles were removed *in-vacuo* yielding a slightly sticky solid. The solid was washed with pentane (200 cm<sup>3</sup>) with attrition being performed, the  
25 washings being removed via cannula filtration. The white solid was dried *in-vacuo* and isolated in the glovebox as a friable white powder. Yield 3.5 g, 59 %. FW = 707.01.

<sup>31</sup>P {<sup>1</sup>H} NMR data:- δ 24 ppm.

- 30 <sup>1</sup>H NMR data:- (400 MHz, CDCl<sub>3</sub>, 298 K) δ 7.59-7.50 (m, 2H, Ar-*H*), 7.09-6.99 (m, 2H, Ar-*H*), 3.01 (d, 4H, <sup>2</sup>J<sub>PH</sub> = 3.2 Hz, CH<sub>2</sub>), 2.07-1.57 (m, 60H, C<sub>10</sub>H<sub>15</sub>) ppm.

<sup>13</sup>C {<sup>1</sup>H} NMR data:- (100 MHz, CDCl<sub>3</sub>, 298 K) δ 139.4 (dd, J<sub>PC</sub> = 10.7 Hz, J<sub>PC</sub> = 2.3 Hz, Ar-C), 131.0 (d, J<sub>PC</sub> = 16.8 Hz, Ar-C), 125.0 (s, Ar-C), 41.1 (d, <sup>2</sup>J<sub>PC</sub> = 10.7 Hz, Ad-C<sup>2</sup>), 37.2 (s,

Ad-C<sup>4</sup>), 36.9 (d, <sup>1</sup>J<sub>PC</sub> = 22.9 Hz, Ad-C<sup>1</sup>), 28.8 (d, <sup>3</sup>J<sub>PC</sub> = 7.6 Hz, Ad-C<sup>3</sup>), 22.0 (dd, <sup>1</sup>J<sub>PC</sub> = 22.9 Hz, <sup>4</sup>J<sub>PC</sub> = 3.1 Hz, CH<sub>2</sub>).

### Vinyl Acetate Carbonylation Examples 1-6

5

#### Example 1

Standard conditions were as follows : In an oxygen free (< 10 ppm O<sub>2</sub>) environment Pd<sub>2</sub>(dba)<sub>3</sub> (22.0mg, 0.04mmoles Pd) and 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (95.0mg, 0.24mmoles) were weighed into a 500ml round bottom flask. To this under a protective atmosphere of nitrogen 300ml of degassed methanol was added, and the solution allowed to stir for one hour. Then methane sulphonic acid (16μl, 0.24mmoles,) was added, along with 0.34g poly vinyl pyrrolidone (PVP) and 75ml vinyl acetate (VAM). This solution was added to an autoclave under vacuum, and heated to 85°C, when 10 bar of CO was added. The gas addition took the temperature to 100°C, where it was held, and the solution allowed to react for 3 hours. The solution was then cooled the pressure released, and the autoclave emptied. A GC sample was taken for analysis.

This experiment was repeated with the same ligand varying the amounts of reactants and the results are set out in Table 3, examples 1-5. Experiment 6 repeats the experiment and uses the adamantyl ligand. Experiment 7 involved the use of 1,2-bis (di-*tert*-butylphosphinomethyl) ferrocene as the ligand.

#### Results

The ligands 1,2-bis(di-*tert*-butylphosphinomethyl)benzene and 1,2-bis(di-*tert*-butylphosphinomethyl)ferrocene when complexed to palladium (II) exhibited catalytic activity for the carbonylation of vinyl acetate. Both the linear and branched products were produced (methyl-2-acetoxy propanoate and methyl-3-acetoxy propanoate), which can be used as precursors to the industrially favourable methyl lactate and 1,3 propanediol. Both ligands



produced an *iso* to normal ratio of two or three to one, with comparable rates. Instead of a high selectivity to the linear product based on the steric bulk of the ligands, the reaction favoured, the branched metal-alkyl intermediate which is the precursor to the hydrolysis/transesterification product methyl lactate.

5

Table 1 shows the effect of temperature on the yield and rate of the reaction for a carbonylation otherwise carried out in accordance with example 1.

Specifically, Example 1 was repeated at varying temperatures and the results are shown in table 1.

10

Table 1 The Effect of Temperature on conversion

Temperature °C	Conversion %	TON (moles product/ mole Pd/hr)
Room Temp (ca 23°C)	5.7	1162
50	65	13260
80	73	14892
100	72	14688

Table 2 shows the effect of pressure on the rate and yield using in other respects the conditions and reactants of Example 1.

15

Table 2 The effect of pressure variation on the Catalysis			
Pressure (bar gauge, including vapour pressure of solvent)		Conversion %	TON (moles product/ mole Pd/hr)
5		50	10312
10		76	15538
20		83	17042

The experiments detailed in table 3 Examples 1-5 were carried out to analyse the effect of the exotherm and the level of various components on the outcome. The experiments were carried out as set out above but with the amounts of components shown in table 3. Generally, the experiments were carried out at 100 °C and take account of the exotherm in maintaining this temperature. However, in examples 2 & 3 the exotherm was not taken into account which causes the experimental temperature to rise to 130 °C. Examples 6 and 7 followed the procedure of example 1 but with the reactant and solvent amounts shown and using the adamantyl and ferrocene ligand respectively.

10

Table 3

Experiment No	Experimental Conditions	Conversion % (total)	TON	Rate (moles i+n/mol Pd/hr)	i:n
1	22mg Pd, 95mg ligand, 300ml MeOH 16ul MeSO <sub>3</sub> H, 0.34g PVP, 75ml VAM 100°C, 3hr, 10bar CO (no exotherm)	66	13464	4488	2:1
2	44mg Pd, 190mg ligand, 300ml MeOH 32ul MeSO <sub>3</sub> H, 1.35g PVP, 50ml VAM 100°C, 3hr, 10bar CO (inc exotherm)	55	3730	1243	3:1
3	44mg Pd, 190mg ligand, 300ml MeOH 64ul MeSO <sub>3</sub> H, 1.35g PVP, 50ml VAM 100°C, 3hr, 10bar CO (inc exotherm)	60	4070	1356	5:1
4	44mg Pd, 190mg ligand, 300ml MeOH 32ul MeSO <sub>3</sub> H, 1.35g PVP, 50ml VAM 100°C, 3hr, 10bar CO (no exotherm)	60	4070	1356	2:1
5	44mg Pd, 190mg ligand, 300ml MeOH 32ul MeSO <sub>3</sub> H, 0.0g PVP, 50ml VAM 100°C, 3hr, 10bar CO (no exotherm)	83	5630	1876	2.5:1
6	22mg Pd, 85mg Ad ligand, 300ml MeOH 16ul MeSO <sub>3</sub> H, 0.34g PVP, 75ml VAM 100°C, 3hr, 10bar CO (no exotherm)	46	9384	3128	2:1
7	22mg Pd, 121mg Me ligand, 300ml MeOH 32ul MeSO <sub>3</sub> H, 1.35g PVP, 50ml VAM	62	8422	2807	2:1

NB "ligand" is 1,2 -bis (di-tert-butylphosphinomethyl) benzene  
 Me ligand is 1,2-bis (di-tert-butyl phosphinomethyl) ferrocene  
 "Ad Ligand" is 1,2 bis (diadamantylphosphinomethyl) benzene  
 Pd is Pd(dba), 19% Pd

Examples 8 and 9 were conducted at low temperature and pressure of CO but with a high catalyst concentration compared with the vinyl acetate. Surprisingly, high conversions were achieved under these conditions. Example 8 was carried out at 30°C and Example 9 at 40°C.

5

### Examples 8 and 9

#### Low temperature, Low CO pressure, High catalyst concentration experiments

Standard conditions for low temperature, high catalyst concentration experiments were as follows : In an oxygen free ( $< 10$  ppm  $O_2$ ) environment  $Pd_2(dba)_3$  23.19% Pd (45.7mg, 0.1mmoles Pd) and 1,2-bis(di-*tert*-butylphosphinomethyl)benzene (157.7mg, 0.4mmoles) were weighed into a 250ml round bottom flask. To this under a protective atmosphere of nitrogen was added methanol (23ml), vinyl acetate (2ml), toluene (530 $\mu$ l) and methanesulphonic acid (29 $\mu$ l, 0.4mmoles). This solution was warmed until all of the solid had dissolved and the flask was then equipped with a cardice condenser and placed in a water bath. The reaction was stirred by means of a magnetic follower and allowed to equilibrate at the water bath set point. Carbon monoxide was bubbled into the stirred solution for a period of 1 minute, by means of a needle introduced via a suba seal in the reaction flask. After this, without altering the carbon monoxide flow rate, the needle was withdrawn from the liquid and the needle was kept well above the liquid level for the remainder of the experiment. In example 8 conducted at 30°C samples were taken at 30 minute intervals for 2 hours and then at hourly intervals up to 5 hours. In example 9 conducted at 40°C samples were taken after 0.5, 1 and 3 hours. The samples were stored at -20C prior to analysis by GC. The results are illustrated in tables 1.0 and 2.0 below.

#### 25 Example 8 30°C

Time (hours)	Conversion	Ratio l:b
0	0	0

0.5	14.5	3.2:1
1.0	24.5	3.2:1
1.5	39.3	3.4:1
2	46.0	3.4:1
3	65.3	3.4:1
4	73.1	3.4:1
5	81.4	3.4:1

#### Example 9 40°C

Time (hours)	Conversion	Ratio l:b
0	0	0
0.5	33.5	3.3:1
1.0	39.6	3.2:1
3.0	70.4	3.2:1

- 5 After distillation of the products of the carbonylation, 2-acetoxy methyl propionate and 3-acetoxy methyl propionate were collected as different distillates.

#### Production of Lactate and 3-hydroxy Esters

##### Preparation of 3 hydroxymethylpropionate

- 10 To 25g of 3 acetoxy methyl propionate (0.171 moles) was added 25g MeOH (0.78 moles) containing 1%w/w methane sulphonic acid . The solution was stirred at 60C for six hours before cooling to room temperature. The sample was analysed by GC, the peak corresponding to 3 acetoxy methylpropionate had completely disappeared and been replaced by a peak corresponding to 3 hydroxymethylpropionate.

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##### Preparation of 2-hydroxymethylpropionate

To 25g of 2 acetoxy methylpropionate (0.171 moles) was added 25g MeOH (0.78

moles) containing 1%w/w methane sulphonic acid. The solution was stirred at 60C for six hours before cooling to room temperature. The sample was analysed by GC, the peak corresponding to 2 acetoxy methylpropionate had completely disappeared and been replaced by a peak corresponding to 2 hydroxymethylpropionate.

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Preparation of 2 hydroxy propionic acid (lactic acid)

To 25g of 2 acetoxy methyl propionate (0.171 moles) was added 25g MeOH. To this stirred solution was added 20g sodium hydroxide (0.5 moles) dissolved in 20 ml of water. The solution was stirred for one hour at 50C before cooling to room temperature. The pH of the solution was then adjusted to pH 3.0 by the slow addition of HCl and the sample stirred for 1 hour. The sample was analysed by GC, the peak corresponding to 2 acetoxy methyl propionate had completely disappeared and been replaced by a peak corresponding to 2 hydroxy propionic acid.

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Preparation of 3 hydroxy propionic acid

To 25g of 3 acetoxy methyl propionate (0.171 moles) was added 25g MeOH. To this stirred solution was added 20g sodium hydroxide (0.5 moles) dissolved in 20 ml of water. The solution was stirred for one hour at 50C before cooling to room temperature. The pH of the solution was then adjusted to pH 3.0 by the slow addition of HCl and the sample stirred for 1 hour. The sample was analysed by GC, the peak corresponding to 3 acetoxy methyl propionate had completely disappeared and been replaced by a peak corresponding to 3 hydroxy propionic acid.

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The reader's attention is directed to all papers and documents which are filed concurrently with or previous to this specification in connection with this application and which are open to public inspection with this specification, and the contents of all such papers and documents are incorporated herein by reference.

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All of the features disclosed in this specification (including any accompanying claims, abstract and drawings), and/or all of the steps of any method or process so disclosed, may be combined in any combination, except combinations where at least some of such features and/or steps are mutually exclusive.

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Each feature disclosed in this specification (including any accompanying claims, abstract and drawings), may be replaced by alternative features serving the same, equivalent or similar purpose, unless expressly stated otherwise. Thus, unless expressly stated otherwise, each feature disclosed is one example only of a generic series of equivalent or similar features.

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The invention is not restricted to the details of the foregoing embodiment(s). The invention extends to any novel one, or any novel combination, of the features disclosed in this specification (including any accompanying claims, abstract and drawings), or to any novel one, or any novel combination, of the steps of any method or process so disclosed.

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